U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207917
Drug Name:	EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5%
Indication(s):	Acne Vulgaris
Applicant:	Galderma
Date(s):	Letter Date: 9/17/2014
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Keywords: Acne vulgaris, single pivotal trial, superiority trial, combination product

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1 EXECUTIVE SUMMARY

The applicant, Galderma, is developing EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% for the topical treatment of acne vulgaris. EPIDUO® (adapalene and benzoyl peroxide) gel, 0.1%/2.5% gel was approved on December 8, 2008 for the indication of topical treatment of acne vulgaris in patients 12 years of age and older (NDA 022320). A supplement for EPIDUO® gel to extend the patient population to cover patients 9 years of age and older was approved on February 1, 2013. Adapalene 0.3% gel as a monotherapy (Differin® 0.3%; NDA 021753) was approved on June 19, 2007.

The applicant submitted data from a single, randomized, multicenter, active- and vehicle-controlled, parallel-group, Phase 3 trial (Study RD.06.SRE.18240). A total of 503 subjects with moderate to severe acne vulgaris were enrolled and randomized from 31 centers (25 in U.S. and 6 in Canada) to EPIDUO FORTE gel, EPIDUO® gel or vehicle gel. EPIDUO FORTE gel was statistically superior (p-values < 0.001) to vehicle gel for all co-primary and secondary efficacy endpoints, see Table 1.

Table 1: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (MI, ITT)

	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)	P-value[(1)]
Co-Primary Endpoints:				
IGA (clear or almost clear): n (%)	73.2 (33.7%)	59.2 (27.3%)	7.6 (11.0%)	<0.001[(2)]
Absolute Change in:				
Inflammatory Lesions: Mean	27.8	26.5	13.2	<0.001[(3)]
Non-Inflammatory Lesions: Mean	40.5	40.0	19.7	<0.001[(3)]
Secondary Endpoints:				
Percent Change in:				
Inflammatory Lesions: Mean	68.7%	69.3%	39.2%	<0.001[(4)]
Non-Inflammatory Lesions: Mean	68.3%	68.0%	37.4%	<0.001[(4)]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by baseline IGA and analysis center using MI methodology (Schafer 1997).
(3) P-value from an ANCOVA model with terms for treatment, analysis center, baseline IGA severity, and baseline lesion counts.
(4) P-value from a CMH test stratified by baseline IGA and analysis center with row mean difference statistic using RIDIT score and MI methodology (Schafer 1997).
MI: Multiple Imputation
ITT: Intent-to-Treat

The applicant stratified the randomization such that 50% of the subjects had moderate acne (IGA = 3) and 50% of subjects had severe acne (IGA = 4) at baseline. In addition, the applicant pre-specified statistical testing (EPIDUO FORTE gel vs. vehicle gel) for the severe acne subgroup in the multiplicity testing strategy. For the severe acne subgroup, EPIDUO FORTE gel was statistically superior (p-values ≤ 0.029) to vehicle gel for the co-primary and secondary efficacy endpoints, see Table 9 on page 11 and Table 14 on page 14 of this review.

INTRODUCTION

1.1 Overview

The applicant, Galderma, is developing EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% for the topical treatment of acne vulgaris. EPIDUO® (adapalene and benzoyl peroxide) gel, 0.1%/2.5% gel was approved on December 8, 2008 for the indication of topical treatment of acne vulgaris in patients 12 years of age and older (NDA 022320). A supplement for EPIDUO® gel to extend the patient population to cover patients 9 years of age and older was approved on February 1, 2013. Adapalene 0.3% gel as a monotherapy (Differin® 0.3%; NDA 021753) was approved on June 19, 2007.

1.1.1 Regulatory History

On May 30, 2012, the Agency and applicant met for a Pre-IND meeting for the proposed new fixed-dose combination under IND (b) (4) For that meeting, the applicant submitted a protocol outline for a Phase 3 trial that contained the following three treatment arms: EPIDUO FORTE gel, adapalene 0.3% monad gel and vehicle gel. During the meeting, the Agency recommended that the 3-arm Phase 3 trial include the approved EPIDUO® gel as a treatment arm instead of the adapalene 0.3% monad; (b) (4) (b) (4) . After the meeting, the applicant phoned the Agency asking if they could file under the existing IND (IND 67801) for the approved EPIDUO® gel. On July 31, 2012, the Agency responded that the applicant can submit protocols and data for the new fixed-dose combination under IND 67801.

On December 5, 2012, the Agency and the applicant met for a Pre-Phase 3 meeting. For that meeting, the applicant submitted a Phase 3 protocol (RD.06.SPR.18240), which had the 3 arms (new fixed-dose gel, EPIDUO® gel and vehicle gel) that the Agency recommended at the Pre-IND meeting. The proposed primary objective of the trial is to demonstrate the superior efficacy of the new fixed-dose combination over the vehicle in the overall population, which consists of 50% moderate and 50% severe, and if this is met, to also demonstrate the same within the severe acne subgroup. The Agency stated:

> (b) (4) relative to a comparator product or in a subgroup of subjects with severe disease would need replication in two studies. The single 3-arm study you propose would not provide adequate information for the proposed subgroup of subjects with severe disease (b) (4)

In response, the applicant stated that they do not plan to claim superiority to the approved EPIDUO® gel, and that they do not plan to include severe acne in the indication.

On January 25, 2013, the applicant submitted the Phase 3 protocol (RD.06.SPR.18240) for Special Protocol Assessment (SPA). The SPA letter was sent to the applicant on March 11, 2013. The letter did not contain any disagreements; however, the letter did contain additional comments regarding randomization (i.e. recommended stratifying by center), handling of missing data, and the regulatory intent of the comparison between the new product and

EPIDUO® gel. On March 29, 2013, the applicant submitted an amended protocol that addressed the Agency's additional comments.

On June 25, 2014, the Agency and the applicant met for a Pre-NDA meeting. The Agency provided general comments on how the data should be submitted (data tabulation datasets, data definition files, annotated case report forms, and analysis datasets).

1.1.2 Clinical Studies Overview

The applicant submitted data from a single pivotal Phase 3 trial (Study RD.06.SRE.18240). An overview of the trial is presented in Table 2.

Table 2: Clinical Study Overview

Location	Study Population	Treatment Arms	Number of Subjects	Dates
U.S. (25 sites) & Canada (6 sites)	Aged 12 years and older, IGA of 3 (moderate) or 4 (severe), 20-100 inflammatory lesions, and 30 to 150 non-inflammatory lesions	EPIDUO FORTE Gel	217	6/12/2013 – 3/25/2014
		EPIDUO Gel	217	
		Vehicle Gel	69	

1.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and entirely electronic. The datasets in this review are archived at the following locations:
\\cdsesub1\evsprod\NDA207917\0000\m5\datasets\18240

2 STATISTICAL EVALUATION

2.1 Data and Analysis Quality

The databases for the studies required minimal data management prior to performing analyses and no request for additional datasets were made to the applicant.

2.2 Evaluation of Efficacy

2.2.1 Study Design and Endpoints

Study 18240 was a multi-center, randomized, double-blind, active- and vehicle-controlled, parallel-group, Phase 3 trial investigating the safety and efficacy of EPIDUP FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% for the treatment of acne vulgaris. For enrollment, subjects must have met the following key inclusion criteria:

- Male or female 12 years of age or older at screening
- Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe), see Table 3 for details on IGA
- 20-100 inflammatory lesions (papules and pustules) on the face (including nose)
- 30-150 non-inflammatory lesions (open comedones and closed comedones) on the face (including the nose)
- ≤ 2 nodules on the face

Randomization was stratified on severity such that 50% of the subjects had an IGA score of 3 (moderate) and 50% of the subjects had an IGA score of 4 (severe). In addition, randomization was stratified by center.

Subjects applied study medication once daily at night for 12 weeks. Subjects were evaluated at screening, baseline and Weeks 1, 2, 4, 8 and 12.

Table 3: Investigator's Global Assessment (IGA) Scale

Grade	Description	
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost Clear	A few scattered comedones and few small papules.
2	Mild	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present.

Source: pg. 114 of protocol for Study 18240

The protocol specified the following co-primary efficacy endpoints:

- Proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) at Week 12
- Absolute change in inflammatory lesion counts from baseline to Week 12
- Absolute change in non-inflammatory lesion counts from baseline to Week 12

The protocol specified the following secondary efficacy endpoints:

- Percent change in inflammatory lesion counts from baseline to Week 12
- Percent change in non-inflammatory lesion counts from baseline to Week 12

2.2.2 Statistical Methodologies

The primary analysis population specified in the protocol was the Intent-to-Treat (ITT) population, defined as all randomized subjects. The protocol also specified supportive analyses using the Per-Protocol (PP) population. The PP population was defined in the protocol as all ITT subjects without major protocol deviations. The protocol specified the following as major protocol deviations:

- Entrance Criteria Deviations: subjects who do not meet one or more major inclusion or exclusion criteria

- Non-Compliance: subjects who have dosing deviations more than 30% of the planned 84 doses (i.e. <59 or >109 doses) or who miss doses for 5 or more consecutive days just prior to the last visit
- Prohibited Medications: subjects who have taken interfering concomitant therapies during post-baseline period
- Administrative error: subjects who have administrative error such as unblinding, medication dispending errors, lesion counts and IGA performed by a non-approved evaluator

The protocol specified a pooling strategy for centers that enrolled less than 7 subjects with severe acne (IGA = 4). By country (U.S. and Canada), these centers were pooled by ordering and combining the smallest with the largest until all centers meet the minimum of 7 subjects with severe acne. After pooling, the pooled and non-pooled centers were designated "analysis centers."

The protocol specified the following hierarchical hypothesis testing of the co-primary endpoints:

1. EPIDUP FORTE gel versus vehicle gel in overall population (i.e., moderate and severe acne subjects)
   - Null Hypothesis: the performance (IGA success, change in inflammatory and non-inflammatory lesion counts) of EPIDUO FORTE gel is the same as vehicle gel
   - Alternative Hypothesis: the performance of EPIDUO FORTE gel is superior to vehicle gel
2. EPIDUO FORTE gel versus vehicle gel in severe acne subgroup
   - Null Hypothesis: within the severe strata, the performance (IGA success, change in inflammatory and non-inflammatory lesion counts) of EPIDUO FORTE gel is the same as vehicle gel
   - Alternative Hypothesis: within the severe strata, the performance of EPIDUO FORTE gel is superior to vehicle gel
3. EPIDUO FORTE gel versus EPIDUO® gel in severe acne subgroup
   - The difference between the new formulation and EPIDUO® gel for the performance measures will be "estimated via a 95% confidence interval". While the applicant listed this comparison as one of "the 3 successive steps in the testing hypotheses", the protocol states "no formal hypothesis testing is planned."

At each step, all co-primary efficacy endpoints will be analyzed. To move from Step 1 to Step 2, the tests for all three co-primary endpoints in Step 1 must be significant (two-sided with $\alpha = 0.05$). To move from Step 2 to Step 3, the tests for all three co-primary endpoints in Step 2 must be significant (two-sided with $\alpha = 0.05$).

The protocol-specified analysis method for the co-primary endpoint of IGA success (i.e., clear or almost clear) at Week 12 was the Cochran-Mantel-Haenszel (CMH) test. For Step 1, the CMH test was stratified by baseline IGA severity and analysis center. For Step 2, the CMH test was stratified by analysis center. The protocol specified investigating the treatment-by-stratum interactions using the Breslow-Day test at $\alpha = 0.10$ level; however, the protocol did not specify a sensitivity analysis if the Breslow-Day test is significant. For Step 3, the protocol specified

calculating the difference in proportions and the confidence interval using the normal approximation (using the method described by Fleiss 1981).

For the co-primary endpoints of absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12, the protocol-specified analysis method was analysis of covariance (ANCOVA) models. For Step 1, the ANCOVA models included the respective baseline lesion counts, treatment, baseline IGA severity, and analysis center as factors. For Step 2, the ANCOVA models included the respective baseline lesion counts, treatment, and analysis center as factors. The protocol specified investigating the treatment-by-stratum interactions in the ANCOVA models at $\alpha = 0.10$ level; however, the protocol did not specify a sensitivity analysis if the interactions are significant. For Step 3, the protocol specified calculating the difference in absolute change in lesion counts and 95% confidence intervals.

For the secondary efficacy endpoints of percent change in inflammatory and non-inflammatory lesion counts from baseline to Week 12, the protocol-specified analysis method was the CMH test row mean difference statistic using RIDIT score, stratified by IGA severity and analysis center. The testing of the secondary endpoints was pre-specified to be conditional on achieving significance of the co-primary endpoints in both the overall population and severe acne subgroup. To control the Type I error rate for testing two secondary endpoints, the protocol specified using the Hochberg procedure. If the p-values for both secondary endpoints are less than 0.05, then both will declared significant. If one p-value was greater than 0.05 (and thus declared non-significant), then the other p-value must be less than 0.025 to be declared significant. It should be noted that percent change in inflammatory and non-inflammatory lesion counts were included in the EPIDUO® label for descriptive purposes.

For the handling of missing data, the primary imputation method specified in the protocol was the multiple imputation (MI) approach. The protocol specified that missing data at Week 12 was to be imputed using a regression model with treatment, reason for discontinuation, and the non-missing data from earlier time-points in the model. Since the regression approach for MI requires monotone missing data (using earlier time-points in the model), the protocol specified using the Markov Chain Monte Carlo (MCMC) approach to impute the non-monotone missing data. The protocol specified a sensitivity analysis for handling of missing data where missing data was imputed using the last observation carried forward (LOCF) approach.

2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 18240 enrolled and randomized a total of 503 subjects (217 to EPIDUO FORTE, 217 to EPIDUO and 69 to vehicle) from 31 centers (25 in U.S. and 6 in Canada). A total of 53 randomized subjects prematurely discontinued from the trial. The discontinuation rates were generally similar across the three treatment arms. The reasons for discontinuation are presented in Table 4. The demographics and baseline disease characteristics are displayed in Table 5. The demographics were generally balanced across the treatment arms; however, subjects in the vehicle gel arm were on average slightly younger than subjects in the other two treatment arms. The baseline disease characteristics were generally balanced across the treatment arms.

Table 4: Disposition of Subjects (ITT)

	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)
Discontinued	20 (9.2%)	25 (11.5%)	8 (11.6%)
Adverse Event	1 (0.5%)	1 (0.5%)	0
Lack of Efficacy	0	0	1 (1.4%)
Lost to Follow-Up	12 (5.5%)	8 (3.7%)	4 (5.8%)
Other	0	1 (0.5%)	0
Pregnancy	0	0	1 (1.4%)
Protocol Violation	1 (0.5%)	2 (0.9%)	0
Subject's Request	6 (2.8%)	13 (6.0%)	2 (2.9%)

Source: Reviewer's Analysis

Table 5: Demographics and Baseline Disease Characteristics (ITT)

	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)
Age			
Mean (SD)	20.1 (7.6)	19.4 (6.8)	18.5 (5.7)
Median	17.0	17.0	16.0
Range	12 – 57	12 – 49	12 – 36
Gender			
Male	104 (47.9%)	103 (47.5%)	33 (47.8%)
Female	113 (52.1%)	114 (52.5%)	36 (52.2%)
Race			
White	171 (78.8%)	166 (76.5%)	52 (75.4%)
Black	35 (16.1%)	37 (17.1%)	13 (18.8%)
Asian	5 (2.3%)	3 (1.4%)	2 (2.9%)
Other	6 (2.8%)	11 (5.1%)	2 (2.9%)
Ethnicity			
Hispanic or Latino	59 (27.2%)	56 (25.8%)	14 (20.3%)
Not Hispanic or Latino	158 (72.8%)	161 (74.2%)	55 (79.7%)
Country			
United States	200 (92.2%)	201 (92.6%)	64 (92.8%)
Canada	17 (7.8%)	16 (7.4%)	5 (7.2%)
IGA			
3 - Moderate	111 (51.2%)	105 (48.4%)	35 (50.7%)
4 - Severe	106 (48.8%)	112 (51.6%)	34 (49.3%)
Inflammatory Lesion Count			
Mean (SD)	39.2 (18.6)	37.7 (16.2)	36.4 (16.5)
Median	32.0	32.0	33.0
Range	20 – 99	20 – 99	20 – 99
Non-inflammatory Lesion Count			
Mean (SD)	58.9 (26.9)	59.9 (29.3)	60.7 (28.2)
Median	52.0	50.0	51.0
Range	30 – 147	30 – 149	30 – 138

Source: Reviewer's Analysis
SD: Standard Deviation

2.2.4 Primary Efficacy Endpoints Results

EPIDUO FORTE gel was statistically superior (p-values < 0.001) to vehicle gel on all three co-primary efficacy endpoints in the overall population. The results from the ITT and PP analyses were similar and are presented in Tables 6 and 7, respectively.

Table 6: Results for the Co-Primary Efficacy Endpoints at Week 12 in the Overall Population (MI, ITT)

	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)	P-value[(1)]
IGA: Clear or Almost Clear	73.2 (33.7%)	59.2 (27.3%)	7.6 (11.0%)	<0.001[(2)]
Absolute Change in Inflammatory Lesions:				
Mean	27.8	26.5	13.2	
LS Mean[(3)]	27.0	26.7	14.4	<0.001[(3)]
Absolute Change in Non-inflammatory Lesions:				
Mean	40.5	40.0	19.7	
LS Mean[(3)]	40.2	39.0	18.5	<0.001[(3)]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by baseline IGA and analysis center using MI methodology (Schafer 1997).
(3) LS means and p-value from an ANCOVA model with terms for treatment, analysis center, baseline IGA severity, and baseline lesion counts.

Table 7: Results for the Co-Primary Efficacy Endpoints at Week 12 in the Overall Population (MI, PP)

	EPIDUO FORTE GEL (N=194)	EPIDUO GEL (N=201)	Vehicle Gel (N=64)	P-value[(1)]
IGA: Clear or Almost Clear	63.8 (32.9%)	55.6 (27.7%)	6.4 (10.0%)	<0.001[(2)]
Absolute Change in Inflammatory Lesions:				
Mean	27.3	25.5	11.7	
LS Mean[(3)]	26.0	25.9	13.3	<0.001[(3)]
Absolute Change in Non-inflammatory Lesions:				
Mean	39.4	39.4	19.0	
LS Mean[(3)]	38.9	38.3	18.0	<0.001[(3)]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by baseline IGA and analysis center using MI methodology (Schafer 1997).
(3) LS means and p-value from an ANCOVA model with terms for treatment, analysis center, baseline IGA severity, and baseline lesion counts.

As stated previously, the applicant stratified the randomization such that 50% of the subjects had moderate acne (IGA = 3) and 50% of subjects had severe acne (IGA = 4) at baseline. In addition, the applicant pre-specified statistical testing (EPIDUO FORTE gel vs. vehicle gel) for the severe acne subgroup in the multiplicity testing strategy. For the severe acne subgroup, EPIDUO FORTE gel was statistically superior (p-values ≤ 0.029) to vehicle gel for the three co-primary

efficacy endpoints. The results for the ITT and PP populations were similar and are presented in Tables 9 and 10, respectively.

Table 9: Results for the Co-Primary Efficacy Endpoints at Week 12 by Baseline Disease Severity (ITT)

	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)	P-value[1]
IGA (clear or almost clear)				
Overall	*33.7%*	*27.3%*	*11.0%*	*<0.001*[4]
IGA = 3 (Moderate)[2]	35.5%	34.5%	10.3%	
IGA = 4 (Severe)[3]	31.9%	20.5%	11.8%	0.029[4]
Absolute Change in Inflammatory Lesions				
Overall	*27.8*	*26.5*	*13.2*	*<0.001*[5]
IGA = 3 (Moderate)[2]	18.8	22.4	12.1	
IGA = 4 (Severe)[3]	37.2	30.2	14.3	<0.001[5]
Absolute Change in Non-Inflammatory Lesions				
Overall	*40.5*	*40.0*	*19.7*	<0.001[5]
IGA = 3 (Moderate)[2]	34.8	35.9	21.5	
IGA = 4 (Severe)[3]	46.3	43.9	17.8	<0.001[5]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) Moderate Sample Sizes = (N_{EF}, N_E, N_V) = (111,105, 35)
(3) Severe Sample Sizes = (N_{EF}, N_E, N_V) = (106,112, 34)
(4) P-value from a CMH test stratified by baseline IGA (overall population only) and analysis center using MI methodology (Schafer 1997).
(5) P-value from an ANCOVA model with terms for treatment, analysis center, baseline IGA severity (overall population only), and baseline lesion counts.

Table 10: Results for the Co-Primary Efficacy Endpoints at Week 12 by Baseline Disease Severity (PP)

	EPIDUO FORTE Gel (N=194)	EPIDUO Gel (N=201)	Vehicle Gel (N=64)	P-value[1]
IGA (clear or almost clear)				
Overall	*32.9%*	*27.7%*	*10.0%*	*<0.001*[4]
IGA = 3 (Moderate)[2]	35.4%	36.3%	9.4%	
IGA = 4 (Severe)[3]	30.2%	19.8%	10.7%	0.058[4]
Absolute Change in Inflammatory Lesions				
Overall	*27.3*	*24.5*	*11.7*	*<0.001*[5]
IGA = 3 (Moderate)[2]	17.8	21.6	11.2	
IGA = 4 (Severe)[3]	37.4	29.0	12.4	<0.001[5]
Absolute Change in Non-Inflammatory Lesions				
Overall	*39.4*	*39.4*	*19.0*	<0.001[5]
IGA = 3 (Moderate)[2]	33.4	35.3	19.5	
IGA = 4 (Severe)[3]	45.7	43.1	18.4	<0.001[5]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) Moderate Sample Sizes = (N_{EF}, N_E, N_V) = (100, 96, 34)
(3) Severe Sample Sizes = (N_{EF}, N_E, N_V) = (94,105, 30)
(4) P-value from a CMH test stratified by baseline IGA (overall population only) and analysis center using MI methodology (Schafer 1997).
(5) P-value from an ANCOVA model with terms for treatment, analysis center, baseline IGA severity (overall population only), and baseline lesion counts.

2.2.5 Handling of Missing Data

Table 11 provides the number of subjects with missing data for the co-primary efficacy endpoints by week and treatment arm. Approximately 9% of the EPIDUO FORTE gel arm, 11% of the EPIDUO® gel arm and 12% of the vehicle gel arm had missing data at Week 12 (i.e., the primary efficacy time-point).

Table 11: Missing Data for the Co-Primary Efficacy Endpoints by Week (ITT)

	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)
Week 1	11 (5.1%)	17 (7.8%)	2 (2.9%)
Week 2	19 (8.8%)	15 (6.9%)	3 (4.3%)
Week 4	10 (4.6%)	16 (7.4%)	3 (4.3%)
Week 8	17 (7.8%)	22 (10.1%)	5 (7.2%)
Week 12	20 (9.2%)	24 (11.1%)	8 (11.6%)

Source: Reviewer's Analysis

For all three co-primary efficacy endpoints, the primary imputation method was the multiple imputation (MI) approach using a regression model with treatment, reason for discontinuation, and the non-missing data from earlier time-points in the model. The protocol also specified using LOCF as a sensitivity analysis for the handling of missing data. For the co-primary endpoint of IGA success, this reviewer conducted an additional sensitivity analysis where missing data was imputed as failures.

Table 12 presents the results for the co-primary efficacy endpoints by the various imputation methods in the overall population. The response rates were slightly higher for the MI approach compared to the other approaches for all three co-primary endpoints; however, EPIDUO FORTE gel was still statistically superior (p-values < 0.001) to vehicle gel for all approaches and endpoints.

Table 12: Results for the Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data in the Overall Population (ITT)

	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)	P-value[1]
IGA (clear or almost clear)				
Multiple Imputation (primary)*	73.2 (33.7%)	59.2 (27.3%)	7.6 (11.0%)	<0.001[2]
LOCF	66 (30.4%)	53 (24.4%)	7 (10.1%)	<0.001[2]
Impute as Failures	66 (30.4%)	52 (24.0%)	7 (10.1%)	<0.001[2]
Absolute Change in Inflammatory Lesions				
Multiple Imputation (primary)*	27.8	26.5	13.2	<0.001[3]
LOCF	25.6	24.0	12.0	<0.001[3]
Absolute Change in Non-Inflammatory Lesions				
Multiple Imputation (primary)*	40.5	40.0	19.7	<0.001[3]
LOCF	37.0	35.9	17.8	<0.001[3]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by baseline IGA and analysis center using MI methodology (Schafer 1997).
(3) P-value from an ANCOVA model with terms for treatment, analysis center, baseline IGA severity, and baseline lesion counts.

Table 13 presents the results for the co-primary efficacy endpoints by the various imputation methods for the severe acne subgroup. For the co-primary endpoint of IGA success, the comparison of EPIDUO FORTE gel to vehicle gel was statistically significant (p-value = 0.029) using the MI approach; however, the comparison was not statistically significant (p-value = 0.068) for LOCF (and imputing as failures). For absolute change in inflammatory and non-inflammatory lesion counts, the values were slightly higher for the MI approach compared to LOCF; however, EPIDUO FORTE gel was statistically superior (p-values < 0.001) to vehicle gel for both approaches and endpoints.

Table 13: Results for the Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data in the Severe Acne Subgroup (ITT)

	EPIDUO FORTE GEL (N=106)	EPIDUO GEL (N=112)	Vehicle Gel (N=34)	P-value[1]
IGA (clear or almost clear)				
Multiple Imputation (primary)*	33.7 (31.9%)	23 (20.5%)	4 (11.8%)	0.029[2]
LOCF	29 (27.4%)	21 (18.8%)	4 (11.8%)	0.068[2]
Impute as Failures	29 (27.4%)	21 (18.8%)	4 (11.8%)	0.068[2]
Absolute Change in Inflammatory Lesions				
Multiple Imputation (primary)*	37.2	30.2	14.3	<0.001[3]
LOCF	34.1	28.2	13.4	<0.001[3]
Absolute Change in Non-Inflammatory Lesions				
Multiple Imputation (primary)*	34.9	35.9	21.5	<0.001[3]
LOCF	32.9	31.0	19.9	<0.001[3]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by analysis center using MI methodology (Schafer 1997).
(3) P-value from an ANCOVA model with terms for treatment, analysis center, and baseline lesion counts.

2.2.6 Secondary Efficacy Endpoints Results

For both the overall population and the severe acne subgroup, EPIDUO FORTE gel was statistically superior (p-values < 0.001) to vehicle gel for both secondary efficacy endpoints. The results for the ITT and PP populations were similar and are presented in Tables 14 and 15, respectively.

Table 14: Results for the Secondary Efficacy Endpoints at Week 12 (MI, ITT)

	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)	P-value[1]
Percent Change in Inflammatory Lesions:				
Overall	*68.7%*	*69.3%*	*39.2%*	*<0.001[2]*
IGA = 3 (Moderate)[3]	63.2%	70.7%	45.3%	
IGA = 4 (Severe)[4]	74.4%	68.0%	33.0%	<0.001[2]
Percent Change in Non-inflammatory Lesions:				
Overall	*68.3%*	*68.0%*	*37.4%*	*<0.001[2]*
IGA = 3 (Moderate)[2]	64.8%	67.6%	43.8%	
IGA = 4 (Severe)[3]	72.1%	68.4%	30.8%	<0.001[2]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by baseline IGA (overall population only) and analysis center with row mean difference statistic using RIDIT score using MI methodology (Schafer 1997).
(3) Moderate Sample Sizes = (N_{EF}, N_E, N_V) = (111,105, 35)
(4) Severe Sample Sizes = (N_{EF}, N_E, N_V) = (106,112, 34)

Table 15: Results for the Secondary Efficacy Endpoints at Week 12 (MI, PP)

	EPIDUO FORTE GEL (N=194)	EPIDUO GEL (N=201)	Vehicle Gel (N=64)	P-value[1]
Percent Change in Inflammatory Lesions:				
Overall	*65.7%*	*66.9%*	*36.0%*	*<0.001[2]*
IGA = 3 (Moderate)[3]	59.5%	68.6%	42.1%	
IGA = 4 (Severe)[4]	72.3%	65.5%	29.2%	<0.001[2]
Percent Change in Non-inflammatory Lesions:				
Overall	*66.3%*	*65.9%*	*35.7%*	*<0.001[2]*
IGA = 3 (Moderate)[2]	62.9%	66.5%	39.2%	
IGA = 4 (Severe)[3]	70.0%	65.4%	31.0%	<0.001[2]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by baseline IGA (overall population only) and analysis center with row mean difference statistic using RIDIT score using MI methodology (Schafer 1997).
(3) Moderate Sample Sizes = (N_{EF}, N_E, N_V) = (100, 96, 34)
(4) Severe Sample Sizes = (N_{EF}, N_E, N_V) = (94,105, 30)

2.3 Evaluation of Safety

2.3.1 Extent of Exposure

The extent of exposure to study product is presented in Table 16. The planned duration of exposure was 12 weeks (84 days). The duration of exposure was similar between the two treatment arms. While the amount of product used was similar between the two active treatment arms, the amount of product use in the vehicle arm was on average less than the two active arms.

Table 16: Extent of Exposure (Safety Population)

	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)
Duration of Exposure (days)			
Mean (SD)	79.0 (19.3)	78.3 (19.2%)	78.4 (17.7)
Median	84	84	84
Range	1 - 100	1 - 99	1 - 94
Duration of Exposure Category			
1 to 14 Days	9 (4.1%)	9 (4.1%)	2 (2.9%)
15 to 28 Days	4 (1.8%)	3 (1.4%)	1 (1.4%)
26 to 56 Days	7 (3.2%)	7 (3.2%)	3 (4.3%)
57 to 70 Days	0	4 (1.8%)	2 (2.9%)
71 to 84 Days	130 (59.9%)	140 (64.5%)	40 (58.0%)
85 to 98 Days	66 (30.4%)	53 (24.4%)	21 (30.4%)
≥ 99 Days	1 (0.5%)	1 (0.5%)	0
Total Amount of Product Used (g)			
N	217	216	69
Mean (SD)	72.8 (57.6)	74.7 (57.1)	57.8 (53.1)
Median	55.6	59.4	43.2
Range	1.5 - 284.3	-12.7 - 284.5	-4.1 - 285.1
Daily Amount of Product Used (g/day)			
N	217	216	69
Mean (SD)	0.92 (0.67)	0.94 (1.05)	0.63 (0.86)
Median	0.74	0.79	0.56
Range	0.06 - 3.34	-9.64 - 4.37	-4.14 - 3.66

Source: pg. 103 and pg. 105 of Clinical Study Report.

2.3.2 Adverse Events

Approximately 23% of EPIDUO FORTE subjects, 19% of EPIDUO® subjects and 19% of vehicle subjects reported at least one adverse event. Table 17 presents an overview of adverse events reporting during the trial. The adverse events reported in at least 1% of subjects in any treatment arm by system organ class and preferred term are presented in Table 18.

Table 17: Overview of Adverse Events Reported (Safety Population)

Subjects With:	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)
Any AEs	50 (23.0%)	42 (19.4%)	13 (18.8%)
Any Drug-related(1) AEs	12 (5.5%)	1 (0.5%)	0
Any Severe AEs	0	0	1 (1.4%)
Any Serious AEs	0	1 (0.5%)	0
Any AEs Leading to Discontinuation	1 (0.5%)	1 (0.5%)	0

Source: pg. 107 of Clinical Study Report.
(1) Drug-related as assessed by the investigator.

Table 18: Adverse Events in >1% of Subjects in any Treatment Group by System Organ Class and Preferred Term (Safety Population)

System Organ Class / Preferred Term	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)
Infections and infestations			
Nasopharyngitis	14 (6.5%)	11 (5.1%)	1 (1.4%)
Upper respiratory tract infection	1 (0.5%)	5 (2.3%)	4 (5.8%)
Influenza	2 (0.9%)	2 (0.9%)	1 (1.4%)
Gastroenteritis	3 (1.4%)	1 (0.5%)	0
Ear infection	0	0	1 (1.4%)
Pharyngitis	0	0	1 (1.4%)
Skin and subcutaneous tissue disorders			
Skin irritation	9 (4.1%)	1 (0.5%)	0
Dermatitis allergic	1 (0.5%)	3 (1.4%)	0
Eczema	3 (1.4%)	0	0
Rash	1 (0.5%)	0	1 (1.4%)
Urticaria	1 (0.5%)	0	1 (1.4%)
Nervous system disorders			
Headache	3 (1.4%)	2 (0.9%)	1 (1.4%)
Dizziness	0	0	1 (1.4%)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (0.5%)	1 (0.5%)	1 (1.4%)
Rhinitis seasonal	0	0	1 (1.4%)
General disorders and administration site conditions			
Fatigue	0	1 (0.5%)	1 (1.4%)
Pyrexia	0	0	1 (1.4%)
Ear and labyrinth disorders			
Motion sickness	0	0	1 (1.4%)
Metabolism and nutrition disorders			
Hypokalaemia	0	0	1 (1.4%)

Source: pg. 110 of Clinical Study Report.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 Gender, Race, Age, and Geographic Region

Tables 19, 20, and 21 presents the results for the co-primary efficacy endpoints (IGA success rate, absolute change in inflammatory lesion counts and absolute change in non-inflammatory lesion counts) by gender, race (white and non-white) and age (12-17 and 18+) subgroups. The treatment effect for both active arms was slightly larger in females than in males. For race, the treatment effect was slightly larger in whites compared to non-whites. For age, the treatment effect measured by IGA success rate was larger in the 18+ subgroup for the two active treatment arms; however, the treatment effect measure by change in lesion counts were generally similar between two age subgroups.

Table 19: Results for IGA Success[(1)] Rate at Week 12 by Gender, Race and Age (ITT)

Subgroup (N_{EF}, N_E, N_V)	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)
Gender			
Male (104, 103, 33)	30.0%	21.2%	9.1%
Female (113, 114, 36)	37.2%	32.8%	12.8%
Race			
White (171, 166, 52)	34.4%	26.5%	8.8%
Non-White (46, 51, 17)	31.3%	29.8%	17.6%
Age			
12-17 (111, 119, 43)	27.7%	24.0%	9.3%
18+ (106, 98, 26)	40.0%	31.2%	13.8%

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) Success is defined as an IGA score of 0 (clear) or 1 (almost clear).

Table 20: Results for Absolute (Percent) Change in Inflammatory Lesion Counts from Baseline at Week 12 by Gender, Race and Age (ITT)

Subgroup (N_{EF}, N_E, N_V)	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)
Gender			
Male (104, 103, 33)	28.3 (66.4%)	25.9 (64.5%)	13.5 (36.2%)
Female (113, 114, 36)	27.3 (70.8%)	27.0 (73.7%)	12.9 (42.0%)
Race			
White (171, 166, 52)	28.3 (69.6%)	26.0 (69.7%)	11.2 (34.6%)
Non-White (46, 51, 17)	26.0 (65.2%)	27.9 (68.1%)	19.2 (53.5%)
Age			
12-17 (111, 119, 43)	28.7 (66.1%)	25.4 (63.9%)	14.0 (39.9%)
18+ (106, 98, 26)	26.9 (71.4%)	27.7 (75.9%)	11.9 (38.2%)

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).

Table 21: Results for Absolute (Percent) Change in Non-Inflammatory Lesion Counts from Baseline at Week 12 by Gender, Race and Age (ITT)

Subgroup (N_{EF}, N_E, N_V)	EPIDUO FORTE Gel (N=217)	EPIDUO Gel (N=217)	Vehicle Gel (N=69)
Gender			
Male (104, 103, 33)	39.9 (68.2%)	38.1 (65.1%)	19.2 (37.4%)
Female (113, 114, 36)	41.0 (68.4%)	41.8 (70.6%)	20.2 (37.4%)
Race			
White (171, 166, 52)	41.1 (69.6%)	40.1 (69.3%)	20.1 (38.9%)
Non-White (46, 51, 17)	38.1 (63.6%)	40.0 (63.9%)	18.5 (32.8%)
Age			
12-17 (111, 119, 43)	42.8 (66.6%)	39.9 (64.9%)	19.6 (32.4%)
18+ (106, 98, 26)	38.0 (70.1%)	40.2 (71.8%)	19.8 (46.5%)

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).

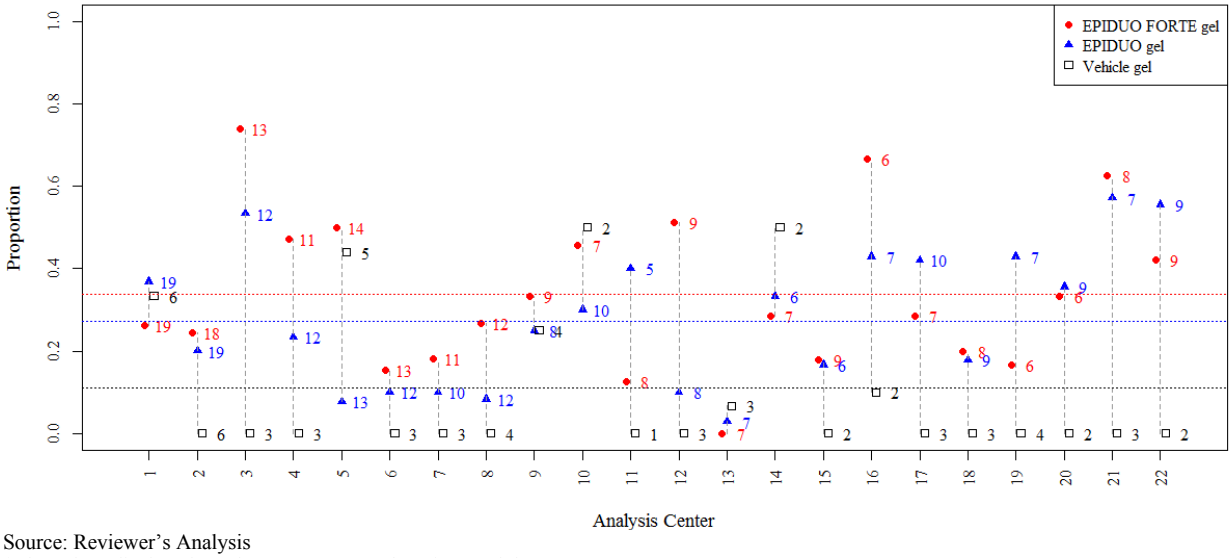
3.2 Center and Country

Study 18240 was conducted at 31 centers (25 in U.S. and 6 in Canada). The protocol specified a pooling strategy for centers that enrolled less than 7 subjects with severe acne. By country, these centers were pooled by ordering and combining the smallest with the largest. For Study 18240, 9 of the 25 centers in the U.S. and all 6 of the centers in Canada enrolled less than 7 subjects with severe acne. The pooling strategy yielded a total of 22 analysis centers (20 U.S. and 2 Canada).

Figures 1, 2 and 3 present the results for the co-primary efficacy endpoints at Week 12 by analysis center. Per the protocol, the applicant conducted the Breslow-Day test for homogeneity of the odds ratio across strata at $\alpha = 0.10$ level for the co-primary endpoint of IGA success rate at Week 12. The p-value for the Breslow-Day test across strata (analysis center and baseline IGA severity) was 0.711. For absolute change in inflammatory and non-inflammatory lesion counts, the protocol specified evaluating the treatment-by-analysis center interaction at $\alpha = 0.10$. The p-values for the interactions were <0.001 and 0.006 for absolute change in inflammatory and non-inflammatory lesion counts, respectively. It should be noted that the protocol did not specify a sensitivity analysis if the interactions are significant. The applicant conducted a set of post-hoc analyses where each analysis center was systematically removed and the p-value for the interaction was obtained to explore the possible source of the interaction effect. This set of post-hoc analyses identified 3 analysis centers (2, 4, and 22). After removing these three analysis centers, the treatment-by-analysis center interactions were no longer significant for both inflammatory and non-inflammatory lesion counts. In addition, EPIDUO FORTE gel was still statistically superior (p<0.001) to vehicle gel with the removal of these three analysis centers.

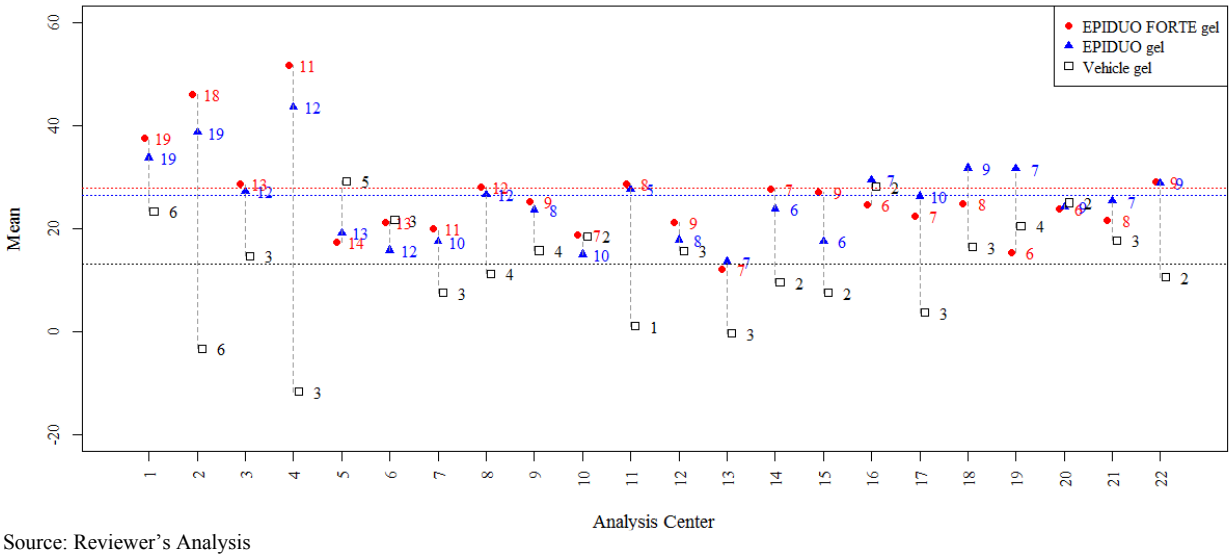
As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. For all three co-primary endpoints, the removal of any one center did not affect the overall conclusions (p-values ≤ 0.001) in the overall population.

Figure 1: Results for the IGA Success at Week 12 by Analysis Center (MI, ITT)



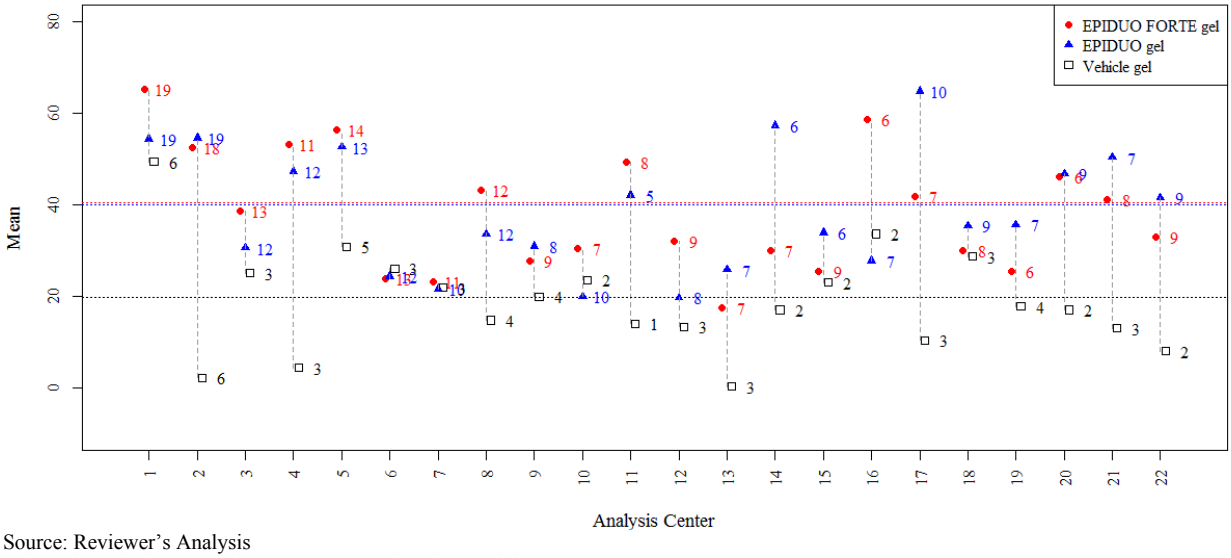
Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).

Figure 2: Results for Absolute Change in Inflammatory Lesion Counts from Baseline at Week 12 by Analysis Center (MI, ITT)



Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).

Figure 3: Results for Absolute Change in Non-Inflammatory Lesion Counts from Baseline at Week 12 by Analysis Center (MI, ITT)



Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).

Table 22 presents the results of the co-primary efficacy endpoints at Week 12 by country (U.S. and Canada). For IGA success and absolute change in non-inflammatory lesion counts, the treatment effect was higher in Canada compared to U.S.; however, only a small proportion of subjects (7.5%) were from Canada.

Table 22: Results for the Co-Primary Efficacy Endpoints at Week 12 by Country (MI, ITT)

Endpoints	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)
IGA (Clear or Almost Clear): n (%)			
U.S.	64.4/200 (32.2%)	50.2/201 (25.0%)	7.6/64 (11.9%)
Canada	8.8/17 (51.8%)	9/16 (56.3%)	0/5 (0%)
Absolute Change in Inflammatory Lesion Counts: Mean			
U.S.	28.0	26.4	13.1
Canada	25.5	27.3	14.8
Absolute Change in Non-Inflammatory Lesion Counts: Mean			
U.S.	40.8	39.6	20.4
Canada	36.7	45.3	11.0

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

There were no major statistical issues affecting overall conclusions. For the handling of missing data, the results in the overall population were generally similar between the primary imputation method (i.e., multiple imputation) and the applicant's pre-specified sensitivity analysis (i.e., LOCF). For the severe acne subgroup, the comparison of EPIDUO FORTE gel to vehicle gel for the co-primary endpoint of IGA success at Week 12 was statistically significant (p-value = 0.029) using the MI approach; however, the comparison was not statistically significant (p-value = 0.068) for LOCF (and imputing as failures).

Treatment effects were generally consistent across subgroups. The applicant's investigation of the treatment-by-center interaction focused on the effects after pooling (i.e., analysis centers). As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. For all three co-primary efficacy endpoints, the removal of any one center did not affect the overall conclusions (p-values ≤ 0.001) in the overall population.

4.2 Collective Evidence

The applicant evaluated the safety and efficacy of EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% in a single, randomized, multicenter, active- and vehicle-controlled, parallel-group, Phase 3 trial (Study RD.06.SRE.18240). The trial enrolled subjects aged 12 years and older, who had an Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe), 20 to 100 inflammatory facial lesions (papules and pustules), and 30 to 150 non-inflammatory facial lesions (open and closed comedones). The protocol-specified co-primary efficacy endpoints were the proportion of subjects with an IGA score of 0 (clear) or 1 (almost

clear) at Week 12, absolute change in inflammatory lesion counts from baseline to Week 12, and absolute change in non-inflammatory lesion counts from baseline to Week 12. The protocol specified two secondary efficacy endpoints: percent change in inflammatory lesion counts from baseline to Week 12 and percent change in non-inflammatory lesion counts from baseline to Week 12. EPIDUO FORTE gel was statistically superior (p-values < 0.001) to vehicle gel for all co-primary and secondary efficacy endpoints in the overall population, see Table 23.

Table 23: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12 (MI, ITT)

	EPIDUO FORTE GEL (N=217)	EPIDUO GEL (N=217)	Vehicle Gel (N=69)	P-value[(1)]
Co-Primary Endpoints:				
IGA (clear or almost clear): n (%)	73.2 (33.7%)	59.2 (27.3%)	7.6 (11.0%)	<0.001[(2)]
Absolute Change in:				
Inflammatory Lesions: Mean	27.8	26.5	13.2	<0.001[(3)]
Non-Inflammatory Lesions: Mean	40.5	40.0	19.7	<0.001[(3)]
Secondary Endpoints:				
Percent Change in:				
Inflammatory Lesions: Mean	68.7%	69.3%	39.2%	<0.001[(4)]
Non-Inflammatory Lesions: Mean	68.3%	68.0%	37.4%	<0.001[(4)]

Source: Reviewer's Analysis
*The values displayed are the averages over the 5 imputed datasets (MI).
(1) EPIDUO FORTE vs. Vehicle
(2) P-value from a CMH test stratified by baseline IGA and analysis center using MI methodology (Schafer 1997).
(3) P-value from an ANCOVA model with terms for treatment, analysis center, baseline IGA severity, and baseline lesion counts.
(4) P-value from a CMH test stratified by baseline IGA and analysis center with row mean difference statistic using RIDIT score using MI methodology (Schafer 1997).

The applicant stratified the randomization such that 50% of the subjects had moderate acne (IGA = 3) and 50% of subjects had severe acne (IGA = 4) at baseline. In addition, the applicant pre-specified statistical testing (EPIDUO FORTE gel vs. vehicle gel) for the severe acne subgroup in the multiplicity testing strategy. For the severe acne subgroup, EPIDUO FORTE gel was statistically superior (p-values ≤ 0.029) to vehicle gel for the co-primary and secondary efficacy endpoints, see Table 9 on page 11 and Table 14 on page 14 of this review.

4.3 Conclusions and Recommendations

Efficacy findings from a single Phase 3 trial (Study RD.06.SRE.18240) established the superiority of EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% over vehicle gel for the topical treatment of acne vulgaris in subjects 12 years of age and older.

SIGNATURES/DISTRIBUTION LIST

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Date: May 14, 2015

Statistical Team Leader: Mohamed Alosh, Ph.D.
Date: May 14, 2015

cc:
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DDDP/Lindstrom
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DDDP/Gould
DDDP/White
DDDP/Robnett
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/s/

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